REMARKS

After entry of the instant amendment, Claims 49-68 and 100-122 are pending and under consideration. A copy of pending Claims 49-68 and 100-122 is attached hereto as *Exhibit A*.

Applicants expressly reserve the right to pursue any canceled subject matter in one or more related, continuation, divisional or continuation-in-part application(s).

I. THE AMENDMENT OF THE CLAIMS

Claims 29-48 and 69-99 have been canceled without prejudice. Applicants expressly reserve the right to pursue any canceled subject matter in one or more related, continuation, divisional or continuation-in-part application(s).

Claims 49, 55, 61 and 65 have been amended to clarify the matter that Applicants regard as their invention. No new matter has been added as a result of these amendments. These amendments are supported in the specification, at, for example, Example II, Table 1 and Table 2.

New Claims 100-122 are fully supported in the specification. Support for new Claims 100-102 can be found in the specification at, for example, page 12, line 34 through page 13, line 6, page 14, lines 4-7 and page 24, lines 18-21. Support for new Claims 103 and 104 can be found in the specification at, for example, page 14, lines 4-7 and page 13, lines 22-25. Support for new Claims 105-107 can be found in the specification at, for example, page 14, lines 4-7 and page 24, lines 21-24. Support for new Claims 108 and 109 can be found in the specification at, for example, page 12, lines 31-33 and page 13, lines 35-36. Support for new Claims 110 and 111 can be found in the specification at, for example, page 12, lines 5-7. Support for new Claims 112-119 can be found in the specification at, for example, page 14, lines 27-37, page 12, lines 5-7, page 12, lines 31-33 and page 13, lines 35-36. Support for new Claims 120-122 can be found in the specification at, for example, page 23, line 36 through page 24, line 6.

As the new Claims 100-122 are fully supported by the specification and claims as originally filed, they do not constitute new matter. Since the new Claims do not constitute new matter and are believed to place the claims in condition for allowance, thereby reducing the number of issues for appeal, entry thereof is therefore respectfully requested.

II. THE REJECTIONS

A. The Rejection of Claims 29-48 and 69-99 Under 35 U.S.C. § 112, First Paragraph (Written Description)

Claims 29-48 and 69-99 are rejected under 35 U.S.C. § 112, first paragraph, for allegedly lacking adequate written description. Applicants respectfully submit that the cancellation of Claims 29-48 and 69-99 renders the rejection moot.

In view of the foregoing, Applicants respectfully request that the rejection of Claims 29-48 and 69-99 under 35 U.S.C. § 112, first paragraph (written description), be withdrawn.

B. The Rejection of Claims 29-79 under 35 U.S.C. § 101

Claims 29-99 are rejected under 35 U.S.C. § 101 for allegedly lacking utility. Applicants respectfully submit that the cancellation of Claims 29-48 and 69-99 renders the rejection of Claims 29-48 and 69-99 moot. Applicants further submit that, as discussed below, Claims 49-68 do not lack utility.

1. The Legal Standard

According to 35 U.S.C. § 101, whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter may obtain a patent therefor subject to the conditions and requirements of 35 U.S.C. The threshold of utility is not high. *See Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700, 1702 (Fed. Cir. 1999). An invention is "useful" under 35 U.S.C. § 101 if it is capable of providing some identifiable benefit. *Id.* (*citing Brenner v. Manson*, 383 U.S. 519, 534, 148 USPQ 689, 695 (1966)).

2. Claims 49-68 Do Not Lack Utility

The symptoms of hereditary hemochromatosis are often similar to those of other conditions, and the severe effects of the disease often do not appear immediately. *See* the Specification at page 3, lines 7-9. Accordingly, it would be desirable to provide a method to identify persons who may be destined to become symptomatic in order to intervene in time to prevent excessive tissue damage associated with iron overload. *See id.* at lines 9-12. One reason for the lack of early diagnosis is the inadequacy of presently available diagnostic

methods to ascertain which individuals are at risk, especially while such individuals are presymptomatic. *See id.* at lines 12-16. The majority of homozygotes and heterozygotes have not been diagnosed. *See id.* at page 1, lines 35-37. Although blood iron parameters can be used as a screening tool, a confirmed diagnosis often employs liver biopsy which is undesirably invasive, costly, and carries a risk of mortality. *See id.* at page 3, lines 16-20.

About 80% - 90% of all hereditary hemochromatosis patients carry at least one copy of the disease-causing 24d1 allele of the hereditary hemochromatosis gene. The 24d1 allele, which is also called the common ancestral mutation, is closely linked to specific alleles of certain genetic markers. *See id.* at page 2, lines 13-22. In the instant Specification, Applicants disclose the location and sequence of 397 previously unknown polymorphisms that are tightly genetically linked to the disease-causing 24d1 allele of the hereditary hemochromatosis gene. Thus, each one of these polymorphisms is a genetic marker for the disease-causing 24d1 allele of the hereditary hemochromatosis gene. Consequently, the claimed polynucleotides, each of which encompasses at least one of these polymorphisms, can be used to determine whether a subject has an increased likelihood of being heterozygous or homozygous for the disease-causing 24d1 allele of the hereditary hemochromatosis gene.

The utility requirement is met when there is evidence of a *reasonable correlation* between what the biological compound has been shown to do and for what it is asserted to be useful. *See, e.g., Nelson v. Bowler*, 206 USPQ 881, 885 (CCPA 1980) ("Relevant evidence is judged as a whole for its persuasiveness in linking observed properties to suggested uses. Reasonable correlation between the two is sufficient . . . ."); *Cross v. Iizuka*, 224 USPQ 739, 747 (Fed. Cir. 1985); *In re Jolles*, 206 USPQ 885 (CCPA 1980); *In re Brana*, 34 USPQ2d 1436 (Fed. Cir. 1995) (emphasis added). The utility of the present invention is to serve as a surrogate marker for the likely presence of the 24D1 mutation in an individual. *See* the Specification at page 12, line 34 through page 13, line 6. In fact, the Utility Examination Guidelines explicitly state that "an isolated . . . DNA molecule may meet the statutory utility requirement if, *e.g.*, it can be used . . . as a marker for a disease gene." 66 Fed. Reg. 1092 at 1094 (response to comment 8). Thus Applicants submit that Claims 49-68 have a specific and credible utility.

In view of the foregoing, Applicants respectfully request that the rejection of Claims 49-68 under 35 U.S.C. § 101 be withdrawn.

C. The Rejection of Claims 29-99 Under 35 U.S.C. § 112, First Paragraph (Enablement)

Claims 29-99 are rejected for allegedly lacking enablement under 35 U.S.C. § 112, first paragraph. The sole basis for this rejection is the alleged lack of utility of the rejected claims. Applicants respectfully submit that the cancellation of Claims 29-48 and 69-99 renders the rejection of Claims 29-48 and 69-99 moot. Further, as explained above, Claims 49-68 have a specific and credible utility.

In view of the foregoing, Applicants respectfully request that the rejection of Claims 29-99 under 35 U.S.C. § 112, first paragraph (enablement), be withdrawn.

CONCLUSION

Applicants respectfully request that the above-made amendments and remarks be considered and made of record in the file history of the instant application. Applicants submit that Claims 49-68 and 100-122 meet all of the criteria for patentability and are in condition for allowance. An early indication of the same is therefore respectfully requested. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

Date: September 19, 2002

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Exhibit A

Serial No.: 08/852,495

Marked up Version of Amended Claims

49. (Amended) An isolated polynucleotide consisting of at least 8 consecutive bases and up to about 100 consecutive bases of the sequence shown in SEQ ID NOS:1 or 2, or the complement thereof, wherein said isolated polynucleotide includes at least one [polymorphic site shown in Table 1] polymorphism selected from a group of polymorphisms at positions 230376, 214795, 207400, 200027, 195404, 160007, 125581, 120853, 96315, 61465, 40431, 38526 and 35983 of SEQ. ID. NO: 1.

55. (Amended) An isolated polynucleotide consisting of at least 18 consecutive bases and up to about 100 consecutive bases of the sequence shown in SEQ ID NOS:1 or 2, or the complement thereof, wherein said isolated polynucleotide includes at least one [polymorphic site shown in Table 1] polymorphism selected from a group of polymorphisms at positions 230376, 214795, 207400, 200027, 195404, 160007, 125581, 120853, 96315, 61465, 40431, 38526 and 35983 of SEQ. ID. NO: 1.

61. (Amended) An isolated polynucleotide consisting of a fragment of at least about 100 consecutive bases and up to about 235 consecutive kilobases of the sequence shown in SEQ ID NOS:1 or 2, or the complement thereof, wherein said isolated polynucleotide includes at least one [polymorphic site shown in Table 1] polymorphism selected from a group of polymorphisms at positions 230376, 214795, 207400, 200027, 195404, 160007, 125581, 120853, 96315, 61465, 40431, 38526 and 35983 of SEQ. ID. NO: 1.

65. (Amended) An isolated polynucleotide consisting of a fragment of at least about 300 consecutive bases and up to about 235 consecutive kilobases of the sequence shown in SEQ ID NOS:1 or 2, or the complement thereof, wherein said isolated polynucleotide includes at least one [polymorphic site shown in Table 1] polymorphism selected from a group of polymorphisms at positions 230376, 214795, 207400, 200027, 195404, 160007, 125581, 120853, 96315, 61465, 40431, 38526 and 35983 of SEQ. ID. NO: 1.

Exhibit B

Serial No.: 08/852,495

Pending Claims After Entry of Instant Amendment

49. (Amended) An isolated polynucleotide consisting of at least 8 consecutive bases and up to about 100 consecutive bases of the sequence shown in SEQ ID NOS:1 or 2, or the complement thereof, wherein said isolated polynucleotide includes at least one polymorphism selected from a group of polymorphisms at positions 230376, 214795, 207400, 200027, 195404, 160007, 125581, 120853, 96315, 61465, 40431, 38526 and 35983 of SEQ. ID. NO: 1.

50. The isolated polynucleotide of Claim 49, wherein the polymorphic site is at base 61465 of SEQ ID NO:1.

51. The isolated polynucleotide of Claim 49, wherein the polymorphic site is at base 35983 of SEQ ID NO:1.

52. A pair of isolated polynucleotides as in Claim 49.

53. A kit comprising an isolated polynucleotide of Claim 49.

54. A kit comprising at least one pair of isolated polynucleotides as in Claim 52.

55. (Amended) An isolated polynucleotide consisting of at least 18 consecutive bases and up to about 100 consecutive bases of the sequence shown in SEQ ID NOS:1 or 2, or the complement thereof, wherein said isolated polynucleotide includes at least one polymorphism selected from a group of polymorphisms at positions 230376, 214795, 207400, 200027, 195404, 160007, 125581, 120853, 96315, 61465, 40431, 38526 and 35983 of SEQ. ID. NO: 1.

56. The isolated polynucleotide of Claim 55, wherein the polymorphic site is at base 61465 of SEQ ID NO:1.

57. The isolated polynucleotide of Claim 55, wherein the polymorphic site is at base 35983 of SEQ ID NO:1.

58. A pair of isolated polynucleotides as in Claim 55.

59. A kit comprising an isolated polynucleotide of Claim 55.

60. A kit comprising at least one pair of isolated polynucleotides as in Claim 58.

61. (Amended) An isolated polynucleotide consisting of a fragment of at least about 100 consecutive bases and up to about 235 consecutive kilobases of the sequence shown in SEQ ID NOS:1 or 2, or the complement thereof, wherein said isolated polynucleotide includes at least one polymorphism selected from a group of polymorphisms at positions 230376, 214795, 207400, 200027, 195404, 160007, 125581, 120853, 96315, 61465, 40431, 38526 and 35983 of SEQ. ID. NO: 1.

62. The isolated polynucleotide of Claim 61 which is cDNA.

63. The isolated polynucleotide of Claim 61 which is RNA.

64. The isolated polynucleotide of Claim 61 which is genomic DNA.

65. (Amended) An isolated polynucleotide consisting of a fragment of at least about 300 consecutive bases and up to about 235 consecutive kilobases of the sequence shown in SEQ ID NOS:1 or 2, or the complement thereof, wherein said isolated polynucleotide includes at least one polymorphism selected from a group of polymorphisms at positions 230376, 214795, 207400, 200027, 195404, 160007, 125581, 120853, 96315, 61465, 40431, 38526 and 35983 of SEQ. ID. NO: 1.

66. The isolated polynucleotide of Claim 65 which is cDNA.

67. The isolated polynucleotide of Claim 65 which is RNA.

68. The isolated polynucleotide of Claim 65 which is genomic DNA.

100. (New) A kit for determining the likelihood of an individual being affected with hereditary hemochromatosis comprising,

(a) one or more oligonucleotides each individually comprising a sequence that hybridizes under stringent hybridization conditions to a nucleic acid comprising one or more polymorphisms at positions 230376, 214795, 207400, 200027, 195404, 160007, 125581, 120853, 96315, 61465, 40431, 38526 or 35983 of SEQ. ID. NO: 1; and

(b) instructions to use the kit to determine the likelihood of said individual being affected with hereditary hemochromatosis.

101. (New) A kit for determining the likelihood of occurrence of a hereditary hemochromatosis mutation in a nucleic acid sample comprising,

(a) one or more oligonucleotides each individually comprising a sequence that hybridizes under stringent hybridization conditions to a nucleic acid comprising one or more polymorphisms at positions 230376, 214795, 207400, 200027, 195404, 160007, 125581, 120853, 96315, 61465, 40431, 38526 or 35983 of SEQ. ID. NO: 1; and

(b) instructions to use the kit to determine the likelihood of occurrence of a hereditary hemochromatosis mutation in said nucleic acid sample.

102. (New) The kit of claim 100 or 101, wherein one or more of the oligonucleotides each individually comprise a sequence that is fully complementary to a nucleic acid comprising one or more polymorphisms at positions 230376, 214795, 207400, 200027, 195404, 160007, 125581, 120853, 96315, 61465, 40431, 38526 or 35983 of SEQ. ID. NO: 1.

103. (New) The kit of claim 100 or 101, further comprising sequencing primers.

104. (New) The kit of claim 100 or 101, further comprising amplification primers.

105. (New) The kit of claim 100 or 101, further comprising reagents for labeling one or more of the oligonucleotides.

106. (New) The kit of claim 100 or 101, wherein one or more of the oligonucleotides are labeled.

107. (New) The kit of claim 106 that includes one or more reagents to detect the label.

108. (New) The kit of claim 100 or 101, wherein one or more of the nucleic acid molecules are each individually complementary to a nucleic acid comprising a polymorphism at position 35983 of SEQ. ID. NO: 1.

109. (New) The kit of claim 100 or 101, wherein one or more of the oligonucleotides are each individually complementary to a nucleic acid comprising a polymorphism at position 61465 of SEQ. ID. NO: 1.

110. (New) The kit of claim 100 or 101, wherein said kit is configured to detect the presence of two or more polymorphisms, wherein at least one of the polymorphisms is selected from a group of polymorphisms at positions 230376, 214795, 207400, 200027, 195404, 160007, 125581, 120853, 96315, 61465, 40431, 38526 and 35983 of SEQ. ID. NO: 1.

111. (New) The kit of claim 100 or 101, wherein said kit is configured to detect the presence of two or more polymorphisms at positions 230376, 214795, 207400, 200027, 195404, 160007, 125581, 120853, 96315, 61465, 40431, 38526 or 35983 of SEQ. ID. NO: 1.

112. (New) An array for determining the likelihood of an individual being affected with hereditary hemochromatosis comprising, one or more oligonucleotides immobilized on a

substrate, wherein each oligonucleotide individually comprises a sequence that hybridizes under stringent hybridization conditions to a nucleic acid comprising one or more polymorphisms at positions 230376, 214795, 207400, 200027, 195404, 160007, 125581, 120853, 96315, 61465, 40431, 38526 or 35983 of SEQ. ID. NO: 1.

113. (New) An array for determining the likelihood of occurrence of a hereditary hemochromatosis comprising, one or more oligonucleotides immobilized on a substrate, wherein each oligonucleotide individually comprises a sequence that hybridizes under stringent hybridization conditions to a nucleic acid comprising one or more polymorphisms at positions 230376, 214795, 207400, 200027, 195404, 160007, 125581, 120853, 96315, 61465, 40431, 38526 or 35983 of SEQ. ID. NO: 1.

114. (New) The array of claim 112 or 113, wherein each oligonucleotide individually comprises a sequence that is fully complementary to a nucleic acid comprising one or more polymorphisms at positions 230376, 214795, 207400, 200027, 195404, 160007, 125581, 120853, 96315, 61465, 40431, 38526 or 35983 of SEQ. ID. NO: 1.

115. (New) The array of claim 112 or 113, wherein one or more of the oligonucleotides are labeled.

116. (New) The kit of claim 112 or 113, wherein one or more of the oligonucleotides are each individually complementary to a nucleic acid comprising a polymorphism at position 35983 of SEQ. ID. NO: 1.

117. (New) The array of claim 112 or 113, wherein one or more of the oligonucleotides are each individually complementary to a nucleic acid comprising a polymorphism at position 61465 of SEQ. ID. NO: 1.

118. (New) The array of claim 112 or 113, wherein said array is configured to detect the presence of two or more polymorphisms, wherein at least one of the polymorphisms is selected from a group of polymorphisms at positions 230376, 214795,

207400, 200027, 195404, 160007, 125581, 120853, 96315, 61465, 40431, 38526 and 35983 of SEQ. ID. NO: 1.

119. (New) The array of claim 112 or 113, wherein said array is configured to detect the presence of two or more polymorphisms at positions 230376, 214795, 207400, 200027, 195404, 160007, 125581, 120853, 96315, 61465, 40431, 38526 or 35983 of SEQ. ID. NO: 1.

120. (New) A kit for determining the likelihood of an individual being affected with hereditary hemochromatosis comprising,

(a) an antibody that specifically binds to a polypeptide encoded by a polymorphic nucleic acid molecules of the invention and

(b) instructions to use the kit to determine the likelihood of said individual being affected with hereditary hemochromatosis.

121. (New) A kit for determining the likelihood of occurrence of a hereditary hemochromatosis mutation in a nucleic acid sample comprising,

(a) an antibody that specifically binds to a polypeptide encoded by a polymorphic nucleic acid molecule of the invention and

(b) instructions to use the kit to determine the likelihood of occurrence of a hereditary hemochromatosis mutation in said nucleic acid sample.

122. (New) The kit of claim 120 or 121, further comprising a reagent for detecting binding of said antibody to said polypeptide.